

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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## **Acknowledgments**

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Table S1. Baseline characteristics of total sample, responders and non-responders in Phase A, and randomized groups in Phase B.

Characteristic	Baseline Characteristic			Characteristic at randomization		
	Total (n=180)	Responders (n=112)	Nonresponders (n=68)	Arm 1 (n=32)	Arm 2 (n=38)	Arm 3 (n=40)
<b>Demographic</b>						
Age in years	79.6 ± 7.6	79.9 ± 7.8	79.1 ± 7.4	80.7 ± 7.9	79.1 ± 8.0	80.3 ± 7.7
Education in years	12.0 ± 3.7	12.1 ± 3.4	11.9 ± 4.1	12.6 ± 4.2	12.0 ± 2.7	12.0 ± 3.2
Female	58.9%	60.7%	55.9%	68.8%	52.6%	60.0%
† Race						
White	71.7%	74.1%	67.6%	81.3%	73.7%	70.0%
African-American	20.6%	18.8%	23.5%	15.6%	18.4%	22.5%
Other	7.8%	7.1%	8.9%	3.1%	7.9%	7.5%
<b>Living Status</b>						
Married	42.2%	39.3%	47.1%	31.3%	36.8%	47.5%
Living at home	55.6%	51.0%	63.2%	43.7%	55.3%	52.5%
Assisted living	22.2%	25.9%	16.2%	31.3%	23.7%	22.5%
Nursing home	22.2%	23.2%	20.6%	25.0%	21.1%	25.0%
<b>Clinical</b>						
Weight in lb	152.9 ± 36.3	153.8 ± 36.3	151.5 ± 36.6	148.7 ± 34.7	154.9 ± 29.4	161.7 ± 30.6
Cholinesterase Inhibitor	61.5%	58.0%	67.2%	59.4%	68.4%	65.0%
Memantine	35.2%	31.3%	41.8%	34.4%	34.2%	25.0%
*Antipsychotic	0%	0%	0%	100%	100%	100%
Anxiolytic/Hypnotic	17.2%	19.6%	13.2%	28.1%	15.8%	20.0%
Antidepressant	23.9%	21.4%	27.9%	15.6%	26.3%	27.5%
Psychosis	80.3%	82.1%	77.3%	12.5%	8.1%	15.0%
Agitation/aggression	80.9%	75.9%	89.4%	9.4%	18.9%	17.5%
NPI Total	36.1 ± 17.0	34.4 ± 16.0	39.1 ± 18.4	9.6 ± 7.8	9.7 ± 10.4	7.9 ± 7.3
NPI Core	16.9 ± 7.3	16.5 ± 6.9	17.6 ± 7.9	2.7 ± 3.4	2.4 ± 3.2	3.0 ± 3.5
Target symptoms	14.8 ± 2.3	14.9 ± 2.3	14.6 ± 2.3	5.7 ± 2.3	5.2 ± 2.0	5.1 ± 2.3
EPS	2.5 ± 3.5	2.1 ± 3.0	3.2 ± 4.2	4.4 ± 4.7	3.2 ± 4.6	2.4 ± 2.6
AIMS	0.2 ± 0.6	0.2 ± 0.5	0.3 ± 0.7	0.2 ± 0.4	0.2 ± 0.7	0.1 ± 0.4
MMSE	13.9 ± 6.4	14.8 ± 6.3	12.5 ± 6.5	13.4 ± 6.6	13.6 ± 6.7	15.5 ± 6.6
ADAS-cog	42.4 ± 15.7	41.3 ± 15.3	44.5 ± 16.4	43.7 ± 15.0	40.9 ± 16.4	39.9 ± 13.8
ADAS-cog (MMSE ≥ 10)	37.2 ± 14.0	36.1 ± 13.1	39.5 ± 15.9	38.8 ± 12.6	34.2 ± 13.7	36.9 ± 11.7
TESS	6.2 ± 4.6	5.4 ± 3.9	7.6 ± 5.4	3.8 ± 2.7	3.4 ± 2.5	2.8 ± 2.1
PSMS	12.6 ± 5.8	12.1 ± 5.7	13.5 ± 5.8	15.1 ± 7.1	12.7 ± 4.7	12.4 ± 4.9

Values: means ± SD or percent. Of 112 responders in Phase A, 110 were randomized in Phase B to Arm 1: risperidone-risperidone, Arm 2: risperidone-placebo, Arm 3: placebo-placebo. † Race was reported by the patient or caregiver; "Other" includes Native American or Native Alaskan (<1% of patients), Asian (2%), Native Hawaiian or other Pacific Islander (<1%), and more than one race (2%). For antipsychotic, anxiolytic/hypnotic and antidepressant, proportions indicate patients who took the medication at baseline (did not washout). \*Eleven patients (9 responders and 2 nonresponders) washed off antipsychotics prior to Phase A; all responders were taking risperidone, an antipsychotic, at randomization. Psychosis: score ≥ 4 on items for NPI delusions or hallucinations. Agitation/aggression: score ≥ 4 on NPI item for agitation/aggression. NPI Total: Neuropsychiatric Inventory, range 0-144, lower scores indicate milder symptoms. NPI Core: sum of NPI items for delusions, hallucinations, and agitation/aggression, range 0-36, lower scores indicate milder symptoms. Target Symptoms: sum of 3 most prominent symptoms of psychosis or agitation/aggression (range 0-18, lower scores indicate milder symptoms). EPS: extrapyramidal signs rated on the Simpson-Angus Scale, range 0-40, higher scores indicate more EPS. AIMS: Abnormal Involuntary Movements Scale, range 0-35, higher scores indicate more tardive dyskinesia. MMSE: Folstein Mini Mental State Exam, range 0-30, higher scores indicate better cognition. ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive total score, range 0-70, higher scores indicate worse cognition (n=166 at baseline). For ADAS-cog in patients with MMSE ≥ 10, n=122 at baseline. TESS: Treatment Emergent Symptoms Scale, range 0-26, higher scores indicate more physical symptoms. PSMS: Physical Self Maintenance Scale, range 1-30, higher scores indicate worse functioning.

Table S2. Adverse events in the total sample, responders and non-responders in Phase A, and sub-groups in Phase B.

Adverse Events number (%)	Phase A: 0-16 weeks			Phase B: 16-48 weeks				
	Total (n=180)	Resp (n=112)	Nonresp (n=68)	R wk 16-32 (n=70)	P wk 16-32 (n=40)	R-R wk 32-48 (n=13)	R-P wk 32-48 (n=27)	P-P wk 32-48 (n=13)
†Serious Adverse Events								
Deaths	3 (2)	0 (0)	3 (4)	1 (1)	1 (3)	1 (8)	0 (0)	0 (0)
Cardiovascular	5 (3)	2 (2)	3 (4)	1 (1)	1 (3)	1 (8)	0 (0)	0 (0)
Neurological	5 (3)	3 (3)	2 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Agitation/aggression	2 (1)	1 (1)	1 (1)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
Pulmonary	2 (1)	1 (1)	1 (1)	1 (1)	1 (3)	0 (0)	0 (0)	0 (0)
Falls, fractures	3 (2)	1 (1)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	5 (3)	1 (1)	4 (6)	2 (3)	2 (5)	0 (0)	0 (0)	0 (0)
*Adverse Events								
Extrapyramidal signs	30 (17)	20 (18)	10 (15)	13 (19)	4 (10)	4 (31)	4 (15)	2 (15)
Akathisia/restlessness	12 (7)	9 (8)	3 (4)	4 (6)	6 (15)	1 (8)	3 (11)	1 (8)
Sedation	20 (11)	14 (13)	6 (9)	7 (10)	5 (13)	1 (8)	1 (4)	1 (8)
Insomnia	4 (2)	5 (5)	5 (7)	3 (4)	1 (3)	0 (0)	1 (4)	0 (0)
Dizziness	4 (2)	2 (2)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	2 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confusion	11 (6)	5 (5)	6 (9)	4 (7)	4 (10)	1 (8)	3 (11)	1 (8)
Agitation/aggression	8 (4)	4 (4)	4 (6)	1 (1)	1 (3)	0 (0)	1 (4)	1 (8)
Fatigue/weakness	3 (2)	1 (1)	2 (3)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Falls	10 (6)	5 (5)	5 (7)	2 (3)	1 (3)	0 (0)	0 (0)	0 (0)
Chest pain/vascular	4 (2)	2 (2)	2 (3)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory	2 (1)	1 (1)	1 (1)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary tract infection	2 (1)	1 (1)	1 (1)	3 (4)	1 (3)	0 (0)	0 (0)	0 (0)
Urinary incontinence	2 (1)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infection of extremity	1 (0.5)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	11 (6)	8 (8)	3 (4)	2 (3)	2 (5)	2 (15)	0 (0)	1 (8)
Constipation	3 (2)	2 (2)	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Weight gain	2 (1)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Dermatitis	1 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Other	11 (6)	8 (8)	3 (4)	3 (4)	1 (3)	0 (0)	1 (4)	1 (8)

Column headings: Resp: responder, Nonresp: Nonresponder, R: risperidone, P: placebo, R-R: risperidone followed by risperidone cell with data on risperidone weeks 32-48, R-P: risperidone followed by placebo cell with data on placebo weeks 32-48, P-P placebo followed by placebo cell with data on placebo weeks 32-48. The number in parentheses is the percent (nearest integer) for that group.

† A serious adverse event was any adverse drug-related event that resulted in any of the following outcomes: death, a life-threatening condition, hospital admission or prolongation of a hospital stay, an unexpected event leading to clinically significant disability or incapacity. The classification of an adverse event as severe was based on the judgment of the investigator and study medical monitor.

\*An adverse event was either (1) report of a clinically significant new adverse event, or (2) worsening from baseline in a symptom to a moderate or severe level rating on the Treatment Emergent Symptoms Scale (TESS). On the Simpson-Angus Extrapyramidal Signs Scale, extrapyramidal signs were rated as an adverse event if there was an average increase of 1 or more (mild symptoms, range 0-4) on the scale compared to baseline, and akathisia/restlessness was rated as an adverse event if there was an increase of 1 or more (range 0-4) on the akathisia/restlessness item on the Simpson-Angus Scale compared to baseline.